

B(1-30)-Arg-A(1-21),

in which B(1-30) and A(1-21) denote the B and A chains of insulin;

- (b) liberating said mini-proinsulin compound from said fusion protein;
- (c) folding and forming disulfide bridges in said mini-proinsulin compound;
- (d) simultaneously incubating said mini-proinsulin compound with trypsin and carboxypeptidase B at a pH of about 6.8 to produce insulin, under conditions where no crystals are formed; followed by
- (e) precipitating the insulin.

REMARKS

Claims 21-23, 25-27, and 31 are pending in the application.

Rejection Under 35 U.S.C. § 112, first paragraph

In paragraph 5, the Examiner rejected claims 21-23 under 35 U.S.C. § 112, first paragraph, alleging that while the specification provides support for the language "expressing in a bacterium a DNA molecule encoding a fusion protein", it does not reasonably provide support for the language "expressing as part of a fusion protein in a bacterium a DNA molecule encoding a mini-proinsulin."

Applicants have amended claims 21 and 22 to more particularly point out and distinctly claim the invention. The claims now read "expressing in a bacterium a DNA molecule encoding a fusion protein which comprises a mini-proinsulin compound."

In paragraph 6, the Examiner rejected claim 32 under 35 U.S.C. § 112, first paragraph, on the basis that the claim does not meet the written description requirement. The Examiner states that the specification does not provide support for making the fusion protein in a single vessel. Without acquiescing in this rejection, Applicants have canceled claim 32. Cancellation of this claim also moots the § 112, first paragraph rejection found in paragraph 7.

In paragraph 8, the Examiner maintained the rejections to claims 21-23, 25-27, and 31 and further rejected claim 32, under 35 U.S.C. § 112, first paragraph, as allegedly not satisfying the written description requirement. The Examiner refers to her argument in the last Office Action, where she stated that the claim limitation "under conditions wherein no crystals are formed" is allegedly new matter as there is nothing in the specification to serve as a basis to exclude conditions where no crystals are formed. Specifically, she states that "this concept does not find support in a single example wherein the conditions are such that no crystals are formed." Applicants traverse this rejection.

One skilled in the art would recognize that crystals would only be formed if the pH was the same as the isoelectric point of the fusion protein. In such a situation, the fusion protein would have exactly the same number of positively and negatively charged amino acid residues, resulting in a net charge of zero and leading to the

precipitation of the fusion protein from the solution. Applicants note, however, that the isoelectric point of the fusion protein of the present invention is about 6.3, while the claims limit the pH to 6.8. Therefore, under these conditions, no crystals can be formed.

Furthermore, and as stated previously, it is well established that the specification need not describe the claimed invention using the identical words found in the claims in order to satisfy the requirements of 35 U.S.C. § 112, first paragraph. *Martin v. Johnson*, 172 U.S.P.Q. 391, 395 (C.C.P.A. 1972). Therefore, Applicants assert that the Office is not applying the proper standards set forth in the case law.

First, the C.C.P.A. has addressed the issue of new matter and ruled that "the issue is not whether a specific new word of a claim was used in the specification as filed, but whether the concept expressed by the word was present." *In re Anderson*, 176 U.S.P.Q. 331 (C.C.P.A. 1973). Accordingly, the issue is not whether the phrase "under conditions where no crystals are formed" has been used in the specification, but whether the concept expressed by this phrase is present in the specification as filed. The Examiner's admission that this limitation is a property of the examples at pages 15-16 is further evidence that the skilled artisan would recognize that no crystals are formed under the conditions described in the specification. Thus, the concept expressed by the disputed phrase is present in the specification as filed.

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FINNEGAN, HENDERSON,
FARABOW, GARRETT
& DUNNER, L.L.P.
1300 I STREET, N.W.
WASHINGTON, D.C. 20005
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In addition, the fact that mono-Arg-insulin is obtained as a precipitate and not in the form of crystals is also confirmed by the crystallization step described in the specification, which is performed after the precipitate is obtained. (Specification at page 16, lines 3-6). Furthermore, in *Tektronix, Inc. v. United States*, 165 U.S.P.Q. 392, 394 (Ct. Cl. 1970), the court ruled that it is not new matter to amend the specification and drawings to make explicit a disclosure which was implicit in the application as filed.

Applicants also refer the Examiner to M.P.E.P. § 2163.07(a).

By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. the application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. *In re Reynolds*, 443 F.2d 384, 170 USPQ 94 (CCPA 1971), *In re Smythe*, 480 F.2d 1376, 178 USPQ 279 (CCPA 1973).

Second, the purpose of the written description requirement is to ensure that Applicants are in possession of the claimed invention as of the date of filing of the application. *Vas-Cath Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). Here, the teachings of the specification described above clearly convey to those skilled in the art that the claimed method of preparing mono-Arg-insulin was indeed in the possession of the Applicants as of the filing date of this application.

Third, Applicants submit that M.P.E.P. § 2173.05(l) is not pertinent. As noted above, the description of process parameters that result in no crystals being formed is the basis for the limitation "where no crystals are formed." The description of such process parameters is not "[t]he mere absence of a positive recitation." On the contrary, it is a specific description of a process where no crystals are formed.

For these reasons, Applicants respectfully traverse this written description rejection under 35 U.S.C. § 112, first paragraph, and request withdrawal of it.

Rejection Under 35 U.S.C. § 103

In paragraphs 10-13, the Examiner continues to maintain the rejections of claims 21-23, 25-27, and 31 under 35 U.S.C. § 103 as allegedly obvious over Markussen et al. (U.S. Patent No. 4,916,212 and EP 0,163,529, hereinafter "the Markussen references"), in view of Goeddel et al. and Grau (U.S. Patent Nos. 4,801,684 and 4,639,332, hereinafter "the Grau references"). The Examiner further cites Mai et al. against claims 25-27 and 31.

In making these rejections, the Office incorrectly interprets the state of the law, reciting that "one cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references." (Office Action at page 17.) This standard does not mean that one cannot point out deficiencies in the prior art references; but that it stands for the proposition that references must not be read in

isolation but for what they fairly teach in combination with the prior art as a whole. *In re Merck & Co., Inc.*, 800 F.2d 1091, 1987 (Fed. Cir. 1986). The law does not stand for the proposition, as the Office asserts, that one cannot criticize the references as not encompassing all of the elements of the claimed invention. In contrast, it is necessary to examine each cited reference to determine whether the requirements of the law are complied with. It is well settled that all claim limitations must be taught or suggested by the prior art. M.P.E.P. § 2143.03. Thus, it is proper to note when a cited reference does not contain a limitation of the present invention, as part of a broader argument that none of the cited references contain the limitation.

In paragraph 10, the Examiner rejects claim 21 under 35 U.S.C. § 103 as allegedly obvious over the Markussen references, in view of Goedell et al. and the Grau references. The Examiner argues that Markussen et al. ('212) discloses insulin precursors that are single peptide chains converted to human insulin by derivatization and treatment with trypsin. The Examiner admits the Markussen references do not specifically teach the preparation of mono-Arg-insulin or the use of trypsin as a cleavage agent for generation of mono-Arg-insulin. The Examiner cites Goeddel et al. as teaching the production of recombinant fusion proteins of insulin precursors with another protein and cleaving them. The Examiner also states that Goeddel et al. teaches production in *E. coli*. The Examiner cites Grau ('684) as using trypsin and

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FINNEGAN, HENDERSON,
FARABOW, GARRETT
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, D. C. 20005
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carboxypeptidase B simultaneously to produce mature insulin from proinsulin. Grau ('332) allegedly teaches that treatment of proinsulin with trypsin alone gives intermediates with an arginine at B31. This derivative allegedly is stable to further tryptic degradation. According to the Examiner, enzymes having both tryptic and carboxypeptidase B activity are required to produce insulin.

The Examiner states that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the intermediate with an arginine at B31 as suggested by Markussen et al. ('212) for the production of mono-Arg-insulin because mono-Arg-insulin is exceptionally stable to further tryptic degradation.

The Office has not established a *prima facie* case of obviousness because the applied references would have failed to:

- teach or suggest the starting materials used in the claimed process;
- teach or suggest the simultaneous addition of trypsin and carboxypeptidase as presently claimed; and
- teach a process of producing mono-Arg-insulin under conditions where no crystals are formed.

Contrary to the assertion of the Office, there is no suggestion to make substitutions from the preferred embodiment of Markussen, nor any reasonable expectation of success in doing so. Markussen discusses a precursor represented by a

generic formula $B(1-29)-(X_nY)_m-A(1-21)$, which includes a very large number of species. In fact, a simple calculation shows that this formula includes millions of possible compounds which may be used as the starting material to produce insulin.

The Federal Circuit has addressed this issue in *In re Baird*, 15 F.3d 380 (Fed. Cir. 1994). In *Baird*, the court stated that a disclosure of millions of compounds does not render obvious a claim to three compounds. *Id.* at 1552. The Court held that there was nothing in the prior art suggesting that one of ordinary skill should select the claimed compound from the numerous compounds contained within the broad genus. Applicants refer to the Patent and Trademark Office's new "Genus-Species Guidelines" (62 F.R. 6217), which became effective on February 11, 1997, changing the Office policy to incorporate the holding in *Baird*. Thus, not complying with the law set forth in *Baird*, the Office has not provided reasons why one would have selected the miniproinsulin as the starting material to produce insulin, especially given the large number of possible compounds included within Markussen's generic formula. Stability of mono-Arg-insulin does not render Applicant's miniproinsulin obvious, since mono-Arg-insulin does not fit within the generic formula of Markussen as suggested by the Examiner.

The Examiner states that Grau ('684) teaches the simultaneous addition of trypsin and carboxypeptidase. (See column 5, lines 49-59.) The Examiner has rejected Applicants' arguments from the prior response distinguishing Grau from the present invention. On page 17, the Examiner states that the argument contrasting the natural porcine proinsulin of Grau from the miniproinsulin of the present invention is not persuasive. The Office, here, alleges that Applicants cannot attack the references individually.

As discussed above, this is a misapplication of the law. It certainly is relevant that Grau does not remedy the deficiencies of Markussen by disclosing the claimed mono-Arg-insulin. Further, Grau describes cleavage of a different compound and there is no assurance and no reasonable expectation of success that this would work with the miniproinsulin of the present invention. The deficiencies in this reference must be considered when evaluating the nonobviousness of the present invention, as no other reference compensates for the deficiency.

Additionally, Applicants wish to point out that Grau carries out the reaction at a pH of 7.2 while the pending claims recite a pH of about 6.8. At 7.2, the pH of the Grau experiment, the enzymes trypsin and carboxypeptidase B are close to or within their optimal range (7.5 to 9 for Trypsin and 7 to 9 for carboxypeptidase B). The present invention, however, takes the novel step of carrying out these reactions at a lower pH,

clearly outside the optimal pH range for the enzymes. Applicants have enclosed product information sheets to support this assertion.

The Examiner states that the limitation of a process of producing mono-Arg-insulin under conditions where no crystals are formed is met by Markussen's ('212)(Examples 15-16, col. 18) demonstration that the processes take place in an aqueous buffer with the isolation of protein via precipitation with acetone. Even if this is correct, arguendo, the Office has not demonstrated that Markussen ('212) in combination with the other references renders obvious the remaining limitations of claim 21. Specifically, the Office has not shown that Markussen ('212) can be combined with other references to render obvious the preparation of mono-Arg-insulin or the use of trypsin as a cleavage agent for generation of mono-Arg-insulin.

In paragraph 11, the Examiner rejected claim 25 under 35 U.S.C. § 103(a) as allegedly obvious over the Markussen references, Goeddel et al., the Grau references, and Mai et al. The Examiner states that Markussen, Goeddel et al., and Grau do not specifically teach the bridging member Met-Ile-Glu-Gly-Arg of step (A) in the claim. According to the Examiner, Mai et al. teach that it would have been well known in the art to use common cleavage sites in fusion proteins. This reference teaches that

cyanogen bromide cleaves after the amino acid methionine and that Xa cleaves after the tetrapeptide Ile-Glu-Gly-Arg. The Examiner states that both Markussen and Goeddel et al. suggest making fusion proteins, which can be cleaved.

In addition to the shortcomings addressed above, claim 25 is not obvious over the prior art as it has a novel and nonobvious bridging member. Here the Office admits that the bridging member is not taught in the prior art; however, indicating in so many words that it would have been obvious to try the combination. The Office fails to show that the prior art suggests this particular member, only pointing to general suggestions regarding fusion proteins. "Obvious to try" is not the state of the law. One skilled in the art must have had a reasonable expectation of success in making the proposed combination. M.P.E.P. § 2143. The Office has, thus, not established the requisite *prima facie* case of obviousness. The short bridging member, however, has the advantage that the proportion of insulin in the fusion protein is relatively high, maximizing the amount of insulin produced via the fusion proteins.

In Paragraph 12, the Examiner rejects claims 22 and 23 under 35 U.S.C. § 103(a) as allegedly obvious over the Markussen references, either in view of Goeddel et al. or the Grau references. The Examiner believes it would have been obvious to use both trypsin and carboxypeptidase B to convert the micro proinsulin of Markussen first to mono-Arg-insulin, and then to insulin.

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FINNEGAN, HENDERSON,
FARABOW, GARRETT
& DUNNER, L.L.P.
1300 I STREET, N.W.
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In addition to the arguments presented above regarding claim 21 above, Applicants believe that the Office has not shown the formation of mono-Arg-insulin as an intermediate. Merely because Grau ('332) teaches that this compound resists further tryptic degradation, the Office has not satisfied its burden. No evidence has been presented regarding the use of this compound *as an intermediate*. Applicants respectfully request the withdrawal of this rejection.

In paragraph 13, the Examiner rejected claims 26-27 and 31-32 under 35 U.S.C. § 103(a) as being unpatentable over the Markussen references, in view of either Goeddel et al., Mai et al., or the Grau references. Again, the Examiner states that it would have been obvious to use both trypsin and carboxypeptidase B to convert the miniproinsulin of Markussen et al. first to mono-Arg-insulin, and then to insulin. Further, according to the Examiner, Grau teaches that mono-Arg-insulin can be formed by trypsin cleavage and that this form is resistant to further tryptic degradation and Grau ('684) teaches that the combination of trypsin and carboxypeptidase B together can convert proinsulin to insulin. Further, as the Examiner has stated above, Markussen et al. and Goeddel et al. allegedly suggest making fusion proteins, and Mai et al. teaches a cleavable sequence such as used in the claimed invention.

The rejection to claim 32 is moot, as the claim has been canceled. With respect to the other claims, the Office has not presented any information in this rejection to compensate for the deficiencies discussed above. Again, the reaction is carried out at a novel and nonobvious pH, and the prior art does not teach or suggest the starting materials of the claimed process, the simultaneous addition of trypsin and carboxypeptidase, and a process where no crystals are formed.

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims. If the Examiner does not believe the claims are in condition for allowance, Applicants request that she contact the undersigned to schedule an interview, by telephoning 202-408-4067.

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To the if further extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this response, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17 which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: M. Paul Barker
M. Paul Barker
Reg. No. 32,013

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^{by}
Carl P. Eivand
Reg. No. 32,220